

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

## A Deep Learning Approach to Anomaly Detection in the Gaia Space Mission Data

### This is the author's manuscript

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1706809> since 2023-01-11T08:25:25Z

*Publisher:*

Ignacio Rojas, Gonzalo Joya, Andreu Catala

*Published version:*

DOI:10.1007/978-3-030-20518-8\_33

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

**Adherence to AIOM (Italian Association of Medical Oncology) lung cancer guidelines in Italian clinical practice: results from the RIGHT-3 (Research for the Identification of the most effective and HIGHly accepted clinical guidelines for cancer Treatment) study**

Sandro Barni<sup>a</sup>, Evaristo Maiello<sup>b</sup>, Massimo Di Maio<sup>c</sup>, Andrea Ardizzoni<sup>d</sup>, Federico Cappuzzo<sup>e</sup>, Ernesto Maranzano<sup>f</sup>, Silvia Novello<sup>c</sup>, Chiara Bennati<sup>g</sup>, Alessandra Ori<sup>h</sup>, Sara Rizzoli<sup>h</sup>, and Lucio Crinò<sup>g</sup>, on behalf of the RIGHT-3 study group.

<sup>a</sup> Azienda Ospedaliera di Treviglio-Caravaggio, Piazzale Ospedale 1, 24047 Treviglio (Bergamo), Italy;

<sup>b</sup> IRCCS Casa Sollievo della Sofferenza, Via Cappuccini, 71013 San Giovanni Rotondo (Foggia), Italy;

<sup>c</sup> Dipartimento di Oncologia, Università di Torino, AOU San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano (Torino), Italy;

<sup>d</sup> Policlinico S Orsola-Malpighi, Via Albertoni 15, 40138 Bologna, Italy;

<sup>e</sup> Istituto Toscano Tumori, Viale Alfieri 36, 57100 Livorno, Italy;

<sup>f</sup> Azienda Ospedaliera Santa Maria di Terni, Via Tristano di Joannuccio 1, 05100 Terni, Italy;

<sup>g</sup> Azienda Ospedaliera di Peruggia, Via S. Andrea Delle Fratte, 06156 Perugia, Italy;

<sup>h</sup> MediData srl, Viale Virgilio 54/U, 41123 Modena, Italy.

**Address for correspondence:**

Prof. Massimo Di Maio  
University of Torino, Department of Oncology  
S. Luigi Gonzaga Hospital  
Regione Gonzole 10, 10043 Orbassano (Torino), Italy  
Phone: +390119026017  
Fax: +390119015184  
e-mail : [massimo.dimaio@unito.it](mailto:massimo.dimaio@unito.it)

## **Abstract**

**Objectives:** Clinical practice guidelines represent a key tool to improve quality and reduce variability of cancer care. In 2004, Italian Association of Medical Oncology (AIOM) launched the RIGHT (Research for the Identification of the most effective and highly accepted clinical guidelines for cancer Treatment) program. The third step, RIGHT3, evaluated the concordance between AIOM lung cancer guidelines and Italian clinical practice.

**Materials and methods:** RIGHT3 was a retrospective observational study, conducted in 53 Italian centers treating lung cancer. Sampling from AIOM database of 230 centers was stratified by presence of thoracic surgery and geographic distribution. To describe the adherence to AIOM guidelines (2009 edition), 11 indicators regarding diagnostic and treatment procedures were identified. Patients with non-small-cell lung cancer (NSCLC) diagnosis who had first visit in 2010 were divided into 3 groups, based on TNM stage: I-II-IIIa (5 indicators), IIIB (3 indicators) and IV (3 indicators).

**Results:** 708 patients were enrolled; 680 were eligible: 225 patients in stage I-II-IIIa; 156 patients in stage IIIB; 299 patients in stage IV. Cyto-histological diagnosis was available in 96%, 97%, 96% of stage I-II-IIIa, IIIB, IV respectively. Positron-emission tomography was performed in 64% of stage I-II-IIIa and 46% of stage IIIB. 88% of stage I-II patients eligible for surgery underwent lobectomy; after surgery, 61% of stage II and 57% of stage IIIa patients received adjuvant chemotherapy. Among stage IIIB patients who received combined chemo-radiotherapy, sequential approach was more common than concomitant treatment (86% vs. 14%). Among stage IV patients, 87% received platinum-based first-line treatment, and 70% received second-line.

**Conclusion:** The RIGHT3 study showed that, in 2010, adherence to Italian NSCLC guidelines was high for many indicators (including those related to treatment of stage IV patients), but lower for some diagnostic procedures. Guidelines adherence monitoring can be useful to reduce variability in cancer care.

**Keywords:** lung cancer; guidelines; treatment; diagnosis

## 1. Introduction

In oncology as well as in other medical specialties, clinical practice guidelines are developed and regularly updated by several national and international health bodies and scientific societies, like the American Society of Clinical Oncology (ASCO) [1-2] and the European Society of Medical Oncology (ESMO) [3-4]. In 2002, following the recommendations of the Italian National Institute of Health (*Istituto Superiore di Sanità*), the Italian Association of Medical Oncology (*Associazione Italiana di Oncologia Medica*, AIOM) established a working group with the aim of developing clinical practice guidelines for cancer treatment. These guidelines were first released in 2002, and thereafter have been annually updated: the most recent update has been released in October 2014, and the next is expected in October 2015. Several factors can influence both the acceptance and the correct use of guidelines: among the most relevant factors, the experience and motivation of physicians, the willingness of patients and the availability of resources [5].

The RIGHT (Research for the Identification of the most effective and HIGHly accepted clinical guidelines for cancer Treatment) project was designed in 2004, with the aim of evaluating how AIOM guidelines are applied in Italian clinical practice. In the RIGHT-1 study, the feasibility and the appropriateness of some indicators were assessed in a limited sample of breast cancer patients, recruited by few selected Institutions [6]. Subsequently, the survey was extended (RIGHT-2 study) and conducted on a higher number of patients with stage I or II invasive breast cancer or stage III colorectal cancer, treated in a large sample of oncology sites throughout Italy [7].

Subsequently, the third step of the RIGHT project (RIGHT-3) was focused on lung cancer. Similarly to other Western countries, lung cancer is the leading cause of tumor-related deaths in Italy [8]. According to a classification commonly used in recent decades, four main histotypes of lung cancer are adenocarcinoma (AC), squamous cell carcinoma (SCC), large-cell lung carcinoma (LCLC) and small cell lung cancer (SCLC). SCC, AC and LCLC have been traditionally grouped together as non-small cell lung cancer (NSCLC), due to similar therapeutic approaches, pathological and biological characteristics and prognosis. The RIGHT-3 study was limited to NSCLC patients, that currently represent about 85% of lung cancers.

In this paper, we report the main results of the RIGHT-3 study, which aimed to evaluate the adherence to AIOM lung cancer guidelines in a large sample of Italian NSCLC patients, , describing the variability of cancer care in this setting. The project was based on the description of adherence to 2009 version of AIOM lung cancer guidelines [9] in the clinical management of patients who received their first visit during 2010. Therefore, the interpretation of the results presented in this paper should take into account that data are referred to that time window. For instance, the indicator of adherence about first-line treatment of advanced disease was the use of platinum-based chemotherapy, and no indicators about molecular characterization and use of targeted agents were used in this project. in fact, gefitinib has been reimbursed in Italy as first-line treatment for advanced NSCLC with Epidermal Growth Factor receptor mutation since May 2011, that is after the period considered in this study. As a general rule, the indicators of adherence to guidelines used in this project were chosen to describe the degree

of variability in both the diagnostic setting and in the multidisciplinary treatment approach.

## 2. Patients and methods

The RIGHT-3 study Steering Committee and members of the AIOM Lung Cancer Guidelines Working Group (see **Appendix I**) designed the study and defined the methods for data collection.

RIGHT-3 was designed as a retrospective observational study, involving a representative sample of AIOM oncology clinical centres across Italy.

A pilot phase confirmed the study feasibility, i.e. the availability of cases and of clinical data. Afterwards, the RIGHT-3 extended phase (hereafter named RIGHT-3 study) was conducted in order to evaluate the agreement between clinical practice and AIOM lung cancer guidelines. As specified in the Introduction, these guidelines are updated every year, and the reference version that was in force when the RIGHT-3 study was conducted was the 2009 version [9].

The involved centers were randomly selected, to be a representative sample of the 230 oncology centers included in the national list identified in 2010 by AIOM. For this purpose, a two-stage sampling was performed: in the first stage, sampling unit were centers; in the second stage, sampling unit were patients. Based on the consideration that the patients with I-II-III A stage carcinoma are usually treated at centres with thoracic surgery unit (TU), while more advanced stages (IIIB, IV) patients management do not necessary need a TU, during the first stage of sampling, sites were randomly collected using a stratified sampling method, where strata were identified by geographic area (Northern, Central and Southern Italy, the latter including Sicily and Sardinia) and availability of TU (with / without TU).



Among centers without TU, ten Institutions were included in the sample without random selection: these units were identified according to the volume of patients managed (at least 50 patients NSCLC / year) and the commitment in lung cancer patients care. The other 16 centers were randomly selected among the remaining centers without TU.

During the second stage, patients were consecutively enrolled from November 2011 until February 2012 with the following inclusion criteria: 1) first visit at oncology center between January and December 2010, in order to exclude patients managed by study centre before AIOM guidelines (2009 edition) entered into force; 2) age  $\geq 18$  years, without upper age limit; 3) diagnosis of NSCLC with TNM staging I-II-IIIA, IIIB or IV (patients with small cell lung cancer were excluded, and staging was considered mandatory because it is crucial for the proper evaluation of AIOM lung cancer guidelines stage-specific recommendations); 4) follow-up by the study center for at least 6 months after diagnosis to assure the availability of patient's relevant information about clinical history and disease management; the patients who died during the 6 months after diagnosis were included in the analysis and the data available until death were collected and analysed. Patients who did not meet the four inclusion criteria listed above were excluded from the analysis.

In order to avoid biases related to the availability of surgical facilities at each participating institution, centers with TU were asked to enrol patients in all stages, while centers without TU were asked to enrol patients in stages IIIB or IV.

To evaluate the adherence to AIOM lung cancer guidelines, three target populations were considered: patients with (i) stage I-II-IIIa, (ii) stage IIIB, (iii) stage IV NSCLC according to pathological (or, if not available, clinical) TNM staging system [10] assessed by the clinical investigators who participated in the study, at the moment they took on responsibility of the patient.

To verify the agreement between guidelines and clinical practice, eleven indicators (five evaluated on stage I-II-IIIa, three on stage IIIB and three on stage IV patients) were identified by the AIOM Lung Cancer Guidelines Working Group. In **Table 1**, these 11 process indicators of lung cancer diagnosis and treatment are reported, along with a synthesis of recommendations included in the 2009 AIOM guidelines for each of the indicators. To minimize the response bias, in addition to random selection of centres and retrospective data collection, the participating centres were not aware of the indicators that had been chosen to assess compliance with guidelines. In order to describe the reasons of non-adherence, each indicator was accompanied by a multiple choice questionnaire, to reveal any reasons for lack of implementation among the following: patient refusal, organizational or technical difficulties, clinician's choice, patient's clinical conditions or other reasons.

The study was approved by the local Ethics Committees of each participating Institution; signed written informed consent was obtained from patients who were still alive during data collection. As for dead patients, Italian Privacy governance gave permission for treating their data without a written informed consent.

Data collection was performed using a web-based interface (each center received a username and a password to access the electronic case report form).

The following data fields were recorded: 1) clinical and socio-demographic characteristics, 2) cancer-related variables such as stage, diagnosis and treatment, 3) care indicators. Onsite monitoring visits were performed in a sample of 13 centers, in order to ensure a proper data source verification of imputed data versus medical charts.

## **2.1. Sample size and Statistical analysis**

The pilot phase was conducted on a convenience sample of 5 AIOM centers, 4 with TU (one in Northern, two in Central and one in Southern Italy) and 1 without TU (located in Northern Italy). In this pilot phase, 22 patients (4 stage I-II-IIIa, 9 stage IIIB and 9 stage IV) were considered.

For the RIGHT-3 study, the number of centers needed for the study, set to 25 with TU and 25 without TU, was defined on the basis of feasibility criteria. In fact, according to the volume of patients managed by the centers involved, it was reasonable to suppose the inclusion of a number of NSCLC patients high enough to allow precise estimates of the outcome of interest, i.e. the proportion of patients adequately treated according to corresponding AIOM lung cancer guidelines.

More in detail, the sample size was planned in order to have an absolute error (i.e. half-width of 95% confidence interval) of 10% at most. Because literature data about adherence to lung cancer guidelines were absent, the results of RIGHT-2 study on adherence to breast and colon-rectal cancer AIOM guidelines were considered. In particular, with a conservative point of view, colorectal cancer guidelines results were considered, because they showed a lower adherence if compared to breast cancer ones. In detail, colorectal cancer guidelines were correctly applied on average in 65% of enrolled patients.

Considering a design effect equal to 2, a percentage of not evaluable patients of 15% and without considering finite population correction, the enrolment of 200 patients for each of the three groups (I-II-IIIA, IIIB, IV stage) was planned. Of course, precision of the estimates would have been lower in the case of a smaller number of patients included: for instance, with half of planned sample size, absolute error would have been higher than 14%.

The main outcome measure was the proportion of patients following recommended guidelines, for each of the 11 indicators. To avoid a possible underestimation of agreement percentage, as denominator of each indicator only the “eligible patients” were considered, i.e., the subgroup of patients for whom application of the recommended procedures was assessable and had no explicit contraindications. The average percentage of agreement for indicators was also calculated within each of three group of patients (I-II-IIIA, IIIB, IV stage) as the ratio between the number of patients who had been treated according to guidelines and the total number of eligible patients for all indicators.

Absolute and relative frequencies were calculated for qualitative data; continuous normally distributed variables were expressed as a mean  $\pm$  SD. Data were analysed using SAS for Windows, release 9.2 (SAS Institute Inc). Project management including data banking, quality control and statistical analysis, was performed by MEDIDATA (Modena, Italy).

### 3. Results

Overall, 53 oncology clinical centers across Italy, 27 with TU and 26 without TU, were involved in the study (47% located in Northern Italy, 25% in Central Italy and 28% in Southern Italy). With respect to the 50 planned centers, the number of centers was intentionally slightly increased, in order to reach the target sample size.

#### 3.1. Stage I-II-IIIa patients

The case records of 233 patients in stage I-II-IIIa were examined and 225 (97%) of them were eligible for the analysis. Among the 8 patients excluded from the analysis, 2 had their first visit to the oncology center outside the eligible period, 3 were not in stage I-II-IIIa and 3 had not a diagnosis of NSCLC. **Table 2** summarizes the main baseline socio-demographic and clinical features of these patients. **Figure 1** shows the distribution of histology at diagnosis by stage. Cyto-histological diagnosis was available in 96% of patients; histotype was NSCLC not otherwise specified in 5% of cases.

##### 3.1.1. Diagnostic procedures

Among non-invasive diagnostic procedures, the more frequently performed were chest computed tomography (87% of evaluable patients) and positron-emission tomography (PET) (64%); among the invasive procedures, the more frequent was fibro-bronchoscopy (42% of evaluable patients) (see **Table 3** for details). Eight patients underwent both PET and mediastinoscopy, six of whom were N1-N2 and two were N0 at diagnosis according to TNM classification [9].

In **Table 1**, the number of eligible patients and the adherence for each lung cancer process indicator are reported. Only 3 patients (2% of stage I-II-IIIa

patients eligible for surgery) underwent exploratory thoracotomy: for this indicator, the adherence was 98%. The more frequent reasons for lack of implementation of diagnosis-related process indicators was clinician's choice (85% and 84% of patients without PET and without mediastinoscopy respectively).

### *3.1.2. Treatment*

Ninety-five per cent of the 153 patients eligible for surgery underwent surgical intervention with little differences among stages (99%, 95% and 88% of stage I, II and IIIA patients, respectively). The lack of surgical intervention was mainly due to patients' conditions (7 out of 8 patients who did not undergo surgery). As detailed in **Table 1**, among the 110 stage I-II operable evaluable patients, 88% underwent lobectomy (81% lobectomy and 7% bi-lobectomy); lobectomy (including bi-lobectomy) was performed on 93% and 81% of stage I and II patients, respectively. Proportion of patients receiving lobectomy / bilobectomy was 77.5% / 8.8% respectively in younger patients, and 90.0% / 3.3% respectively in elderly patients.

Ninety-nine stage II or IIIA patients underwent surgical intervention (in detail 46 stage II and 53 stage IIIA); 59% of them subsequently received adjuvant chemotherapy (61% and 57% of stage II and IIIA, respectively). Patients did not undergo adjuvant chemotherapy for the following reasons: patient's clinical conditions (43% of patients with available reason), negative lymph nodes (17%), clinician's choice (13%), patient refusal (10%) or other reasons (a combination of the above mentioned). Proportion of patients receiving adjuvant chemotherapy was 67.1% and 34.6% among younger and elderly patients,

respectively. Patient's general conditions were the most common reason for the exclusion of elderly patients.

### 3.2. Stage IIIB patients

The case records of 169 stage IIIB lung cancer patients were examined, and 156 (92%) of these were eligible for the analysis. Among the 13 patients excluded from the analysis, 1 had the first visit to the oncology centre outside the period January-December 2010, 1 was not followed-up by the study center for at least 6 months after diagnosis, 12 were not stage IIIB (the same patient could have more than one violations). In **Table 2**, main baseline socio-demographic and clinical features of the eligible patients are shown. Cytological diagnosis was available in 97% of patients; histotype was NSCLC not otherwise specified in 13% of cases.

#### 3.2.1. Diagnostic procedures

Among non-invasive diagnostic procedures, the more frequently performed were chest computed tomography (87% of evaluable patients) and PET (46%); among the invasive procedures, the more frequent was fibro-bronchoscopy (51% of evaluable patients) (see **Table 3** for details). Considering the sixty-seven patients who did not undergo PET with explicit reason for non-execution, the more frequently provided motivation was clinician's choice, alone (78%) or combined with other reasons, such as patient's refusal or technical difficulties (7%).

#### 3.2.2. Treatment

Sixteen patients (11% of evaluable ones) underwent surgical intervention, 75% of whom after mediastinoscopy or PET. Ninety-four per cent of evaluable patients received a first, second or third line chemotherapy treatment. As

depicted in **Figure 2**, the more frequent first-line treatment was chemotherapy alone (64% of evaluable patients) or in combination with radiotherapy (28%) or targeted therapy (1%). Considering patients with a chemo-radiotherapy first-line treatment, 14% and 86% of them underwent a concurrent and sequential therapy, respectively (**Table 1**). Sequential treatment was much more common than concurrent approach, independently of age (88.0% and 83.3% in younger and elderly patients, respectively).

One-hundred forty-six patients had a first-line chemotherapy or targeted therapy: 79% received a combination chemotherapy, 15% a single-agent chemotherapy and 6% a targeted therapy (with or without chemotherapy agents). Details of the first-line chemotherapy and targeted therapy are reported in **Table 4**.

### 3.3. Stage IV patients

The case records of 306 stage IV lung cancer patients were examined, and 299 (98%) of them were eligible for the analysis. Among the 7 patients excluded from the analysis, 4 had the first visit to the oncology center outside the period January-December 2010, 1 was not followed-up by the study center for at least 6 months after diagnosis, 1 was not stage IV and 1 had not a NSCLC diagnosis. In **Table 2**, main baseline socio-demographic and clinical features of the 299 patients are reported. Cyto-histological diagnosis was available in 96% of cases; histotype was NSCLC not otherwise specified in 13% of patients.

#### 3.3.1. Diagnostic procedures

Among non-invasive diagnostic procedures, the more frequently performed were chest computed tomography (91% of evaluable patients) and PET (44%);



among the invasive procedures, the more frequent was fibro-bronchoscopy (41% of evaluable patients) (see **Table 3** for details).

### *3.3.2. Treatment*

The more frequent first-line treatment was chemotherapy alone (72% of evaluable patients) or in association with radiotherapy (15%) or targeted therapy (3%) (see **Figure 2**). All lung cancer process indicators selected for stage IV patients were about therapy (see **Table 1**): more in detail, 87% of first-line chemotherapy treated patients had a platinum-based regimen treatment and 70% of patients treated with first-line chemotherapy received a second-line treatment. Two-hundred seventy-six patients had a first-line chemotherapy or targeted therapy, 70% of whom had a combination chemotherapy, 14% a single-agent chemotherapy and 15% a targeted therapy (with or without chemotherapy agents). Details of the first-line chemotherapy and targeted therapy administered are reported in **Table 4**. Considering the 90 patients older than 70 years, 94% of them were treated with chemotherapy (irrespective of the line), while the proportion of younger patients treated with chemotherapy ranged between 100% for patients aged 30-40 and 40-50 years to 95% for patients 60-70 years old.

## **3.4. Summary of adherence**

Globally, on average, 67%, 39% and 81% of stage I-II-III A, IIIB and IV patients respectively received recommended care according to the lung cancer indicators chosen for the study; the higher adherence was observed for the proportion of stage I-II-III A patients who did not undergo exploratory thoracotomy (98%) and for the proportion of stage IV patients older than 70

years who underwent chemotherapy (94%). On the other hand, the lower adherence was observed for the proportion of stage III patients eligible for surgery who underwent mediastinoscopy (7%).

#### **4. Discussion**

In principle, the successful implementation of clinical practice guidelines should lead to an improvement in quality of health care, by decreasing inappropriate heterogeneity among different Institutions and different physicians, and expediting the application of effective improvements to clinical practice [5, 11]. Previous phases of the RIGHT project had described the adherence to clinical practice guidelines issued by Italian Association of Medical Oncology (AIOM) in breast cancer and colorectal cancer patients [6,7]. In the present analysis, we reported the evaluation of the adherence to specific AIOM clinical practice guidelines in a large sample of Italian patients affected by NSCLC.

In the group of stage II and III patients who underwent surgery, proportion of subjects who subsequently received adjuvant chemotherapy in our analysis was 59%. This proportion appears reasonable, considering that the most common reason for exclusion of patients from administration of adjuvant treatment, as declared by physicians, was their unfit clinical condition. After the publication of pivotal trials showing the efficacy of adjuvant chemotherapy, its penetration in daily clinical practice has significantly increased, although necessarily limited to a selected proportion of patients [12,13]. A previous survey conducted in 2009 among Italian oncologists about the use of adjuvant treatment for NSCLC patients showed that, in principle, the majority of physicians considered the indication for adjuvant chemotherapy in clinical practice [14]. However, given the tolerability profile of platinum-based treatment, many patients could be judged unfit for treatment in clinical practice, due to age, clinical conditions, post-

operative length of hospital stay, comorbidities [15]. Our data confirm this limitation.

In the subgroup of stage IIIB patients studied in our analysis, the vast majority of subjects did not receive a concurrent chemo-radiotherapy treatment, and were treated with a sequential approach. According to literature, use of concurrent chemo-radiotherapy, as compared with sequential approach, is associated with improved survival, at the cost of increased acute esophageal toxicity [16]. The choice of a less toxic approach could justify, at least in part, the low use of concomitant treatment in Italian clinical practice. Furthermore, in some cases, radiotherapy could be delayed due to logistic reasons, or due to a specific medical decision, with the intention of obtaining a tumor shrinkage with chemotherapy before administering radiation therapy. In a survey conducted in 2009 by the Italian Society of Radiation Oncology Lung Cancer Study Group among all Italian radiation oncology institutions, upfront concomitant radio-chemotherapy was used in only 14% of cases, that is very similar to the proportion reported in the present analysis. Notably, in that survey, 53% of the institution declared that patients have a clinical examination by a radiation oncologist only after the beginning of chemotherapy, having already received 2-4 cycles of chemotherapy in 82% of cases [17].

In the subgroup of patients with advanced disease, adherence to guidelines, at least for the indicators chosen in this study, was high. Notably, the vast majority of elderly patients received chemotherapy, confirming that age itself is no more considered a barrier to receive active anti-cancer treatment. This is reassuring and coherent with the fact that important randomized trials,

demonstrating the feasibility and the efficacy of chemotherapy in elderly patients with advanced NSCLC, were conducted in Italy in the last decades [18,19].

## **5. Conclusions**

In conclusion, the RIGHT-3 project showed an encouraging application of guidelines in Italian clinical practice for patients with NSCLC; for most of the indicators, with some relevant exceptions, like the low diffusion of mediastinoscopy in the diagnostic phase of stage III operable patients and the very low application of concurrent chemo-radiotherapy for locally advanced disease. Some of these exceptions deserve a specific comment: the use of mediastinoscopy, for example, has experienced a “physiological” reduction in recent years, due to the increasing diffusion of minimally invasive endosonography procedures (transesophageal and endobronchial ultrasound) that allow avoiding further procedures when nodal metastases are found at endosonography [20].

In principle, there can be many reasons for sub-optimal adherence to guidelines in clinical practice [21]. With the production and the periodical, regular update of guidelines, that are freely available on the association website, AIOM has the objective of reducing the barriers related to guidelines awareness and knowledge in Italy. Furthermore, this kind of analysis is useful to describe and understand the other potential barriers for an optimal application of guidelines in daily practice (for instance related to external factors, logistical issues or lack of resources), with the aim of further improving quality and homogeneity of patients' management.

## **Acknowledgments**

This research was sponsored by a grant from Eli Lilly, that had no role in data collection, data interpretation and manuscript writing. We are grateful to MediData (Modena, Italy) for data collection and statistical analysis.

**Conflicts of interest**

The authors declare they have no relevant conflicts of interest for this paper.

## **1. Appendix I: The RIGHT-3 study group**

### Member of the AIOM guidelines Working Group

- Sandro Barni, Ospedale Treviglio-Caravaggio, Bergamo
- Evaristo Maiello, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia

### Scientific secretary of the AIOM Lung Cancer guidelines

- Massimo Di Maio, Dipartimento di Oncologia, Università di Torino, AOU San Luigi Gonzaga, Orbassano (TO)

### Steering Committee:

- Lucio Crinò, Azienda Ospedaliera Perugia, Perugia
- Andrea Ardizzoni, Azienda Ospedaliero-Universitaria di Parma, Parma
- Federico Cappuzzo, Ospedale di Livorno, Livorno
- Ernesto Maranzano, Azienda Ospedaliera Santa Maria di Terni, Terni
- Silvia Novello, Dipartimento di Oncologia, Università di Torino, AOU San Luigi Gonzaga, Orbassano (TO)

### Participating centres:

- Oncologia Medica Ospedale Treviglio-Caravaggio, Treviglio (Bergamo): Sandro Barni, Fausto Petrelli
- U.O. Oncologia A.O.U. Arcispedale Sant'Anna, Ferrara: Elena Raisi, Antonio Frassoldati, Alessandra Santini, Patrizia Longo
- Oncologia Ospedale S. Spirito, Casale Monferrato (Alessandria): Mario Botta, Maria Vittoria Oletti, Gabriele Biaggi, Alberto Muzio, Elisabetta Gattoni, Lorena Giarretto, Emiliana Bertoldo
- Oncologia Ospedale Civile, Saluzzo (Cuneo): Davide Perroni, Ivan Facilissimo, Lucia Evangelisti
- S.C. Oncologia Ospedale Santa Maria degli Angeli, Pordenone: Alesssandro Del Conte, Antonino Ius
- S.C. Oncologia Ospedale Regionale U.Parini, Aosta: Gianmauro Numico, Antonella Cristofano, Cristina Barè
- Oncologia Ospedale del Delta, Lagosanto (Ferrara): Pierluigi Ballardini, Guido Margutti
- U.O. Oncologia Medica Azienda Ospedaliera di Parma, Parma: Marcello Tiseo, Roberta Camisa, Elena Rapacchi, Marco Bartolotti
- U.O. Oncologia Medica Ospedale San Gerardo, Monza (Monza e Brianza): Diego Cortinovis, Monica Perez Gila
- S.S. Tumori Polmonari IST Istituto nazionale per la ricerca sul cancro, Genova: Francesco Grossi, Caterina Donato, Maria Giovanna Dal Bello, Erika Rijavec, Giulia Barletta, Carlo Genova, Nidia Diaz, Claudio Sini
- Oncologia Medica Arcispedale S. Maria Nuova, Reggio Emilia: Corrado Boni, Francesca Zanelli, Roberta Gnoni, Giovanna Stridi, Elena Magnani, Erika



- Gervasi, Silvia Fanello
- Oncologia Ospedale di Romano Lombardia, Romano Lombardia (Bergamo): Veronica Lonati, Fausto Petrelli, Marco Cremonesi
  - S.C. Oncologia Azienda Ospedaliera Universitaria, Trieste: Guido Del Conte, Angela Dicorato
  - Oncologia Medica Ospedale Santa Chiara, Trento: Orazio Caffo, Viviana Murgia, Antonello Veccia
  - Oncologia Az. Osp. Sant' Anna, San Fermo della Battaglia (Como): Monica Giordano, Micol Gilardoni, Micol Luchena
  - Oncologia Medica Ospedale Centrale, Bolzano: Emanuela Vattermi
  - Oncologia Az. Osp. Univ. Policlinico, Modena: Fausto Barbieri, Laura Marra, Elisa Pettorelli,
  - U.O. Oncologia Medica Fondazione Poliambulanza Istituto Ospedaliero, Brescia: Maria Giuseppina Mazzocchi, Fausto Meriggi
  - Chirurgia Toracica Istituto Europeo di Oncologia, Milano: Lorenzo Spaggiari, Piergiorgio Solli
  - U.O. Oncologia Medica Policlinico S.Orsola Malpighi, Bologna: Andrea Angelo Martoni, Barbara Melotti, Claudia Degli Esposti
  - Dipartimento di Oncologia IRST di Meldola, Meldola (Cesena – Forlì): Dino Amadori, Manuela Monti, Carlo Milandri
  - Oncologia Medica Ospedale Ca' Foncello, Treviso: Giovanni Rosti, Matteo Bertolin, Laura McMahon
  - Oncologia Ospedale San Giovanni Addolorata, Roma: Maria Mauri, Olga Martelli
  - Dh Oncologia Ospedale del Ceppo, Pistoia: Marco Di Lieto, Miriam Ricasoli
  - U.O. Oncologia Ospedale Civile di Avezzano, Avezzano (L'Aquila): Francesco Recchia, Anna Di Blasio, Giampiero Candeloro
  - Oncologia Medica Ospedale Campo di Marte, Lucca: Editta Baldini, Manuela Pellegrini, Erika Coppi, Giovanna Cirigliano
  - Oncologia Medica Ospedale SS Annunziata, Chieti Scalo: Michele Tursi, Stefano Iacobelli, Luciana Irtelli, Jamara Giampietro, Nicola Tinari
  - Clinica di Oncologia Medica Az. Osp. Ospedali Riuniti Umberto I, Salesi, Lancisi, Ancona: Stefano Cascinu, Rossana Berardi, Alessandra Lucarelli, Chiara Pierantoni, Azzurra Onofri, Michela Burattini
  - S.C. Oncologia Medica Azienda Ospedaliera Perugia, Perugia: Lucio Crinò, Fabiana Marchetti, Rita Chiari, Chiara Bennati
  - S.C. Oncologia Medica I A.O.U. Ospedale Careggi, Firenze: Francesco Di Costanzo, Fabiana Cecere, Cristina Prabha Ranchicchio, Francesca Mazzoni
  - U.O. Oncologia medica Ospedale Vittorio Emanuele III, Castelvetro (Trapani): Liborio Cristina, Liboria Travagliato
  - U.O. Oncologia P.O. Occidentale asl TA1, Castellaneta (Taranto): Antonio Rinaldi, Stefania Bruno
  - Oncologia Medica e Terapie Integrate A.O.U. Policlinico G. Martino, Messina: Vincenzo Adamo, Tindara Franchina, Claudia Proto
  - Oncologia Ospedale San Gennaro, Napoli: Luigi Maiorino, Manuela Musicò
  - Oncologia Ospedale Giovanni Paolo II, Olbia (Olbia – Tempio): Salvatore Ortu, Carlo Putzu

- Oncologia Medica IRCCS Giovanni Paolo II, Bari: Domenico Galetta, Annamaria Catino, Daniele Rizzi
- Oncologia Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG): Giuseppe Palomba, Giovanna Capuano
- Oncologia Az. Osp. Bianchi Melacrino Morelli, Reggio Calabria: Giuseppe Bellocco, Mario Nardi, Rocco Giannicola, Antonella Falzea
- U.O.C. Oncologia A.O.R.N. Cardarelli, Napoli: Giacomo Carteni, Roberto Fiorentino, Manuela Otero, Andrea Planeta,
- Oncologia Medica Ospedale Civile, Belluno: Petros Giovanis
- S.O.C. Oncologia Medica Ospedale Cardinal Massaia, Asti: Franco Testore, Marco Ceste, Diego Dongiovanni
- U.O.S. Oncologia Az. Ospedale Villa Scassi - ASL 3 Genovese, Genova: Manlio Mencoboni
- Oncologia Medica Università Campus Bio Medico, Roma: Giuseppe Tonini, Salvatore Intagliata, Cinzia Potestà
- Immunoterapia Oncologica Az. Osp. Univ. Senese, Siena: Michele Maio, Luana Calabrò, Diego Annesi
- U.O. Oncologia Medica AO Garibaldi Nesima, Catania: Roberto Bordonaro, Laura Longhitano
- U.O.C. Oncologia Medica Ospedale Civile SS. Annunziata, Sassari: Antonio Contu, Marianna Contu, Antonio Pazzola
- Oncologia Medica Pad.oncologico Ospedale V. Fazzi, Lecce: Vito Lorusso, Luciana Petrucelli, Giampiero Romano, Abbondanza Gambino
- Oncologia Medica Ospedale Civico, Palermo: Biagio Agostara, Giuseppina Savio
- Oncologia Medica USL 8 Ospedale del Valdarno, Montevarchi (Arezzo): Alessandra Signorini, Marianna Turrini
- U.O. Oncologia Medica Ospedale Madonna del Soccorso, San Benedetto del Tronto (Ascoli Piceno): Giorgio De Signoribus, Manuela Brugni
- Oncologia Ospedale di Livorno, Livorno: Federico Cappuzzo, Elisa Lani, Lorenza Landi, Gabriele Minuti, Armida D’Incecco
- U.O. Oncologia Ospedale Mariano Santo, Cosenza: Salvatore Palazzo, Salvatore Turano, Rosalbino Biamonte, Caterina Manfredi
- U.O.C. di Oncologia Medica Ospedale Maria Paternò Arezzo, Ragusa: Carmelo Iacono, Sara Licitra

#### Project Management, Statistical Analyses and data management:

MediData Studi e Ricerche, Modena:

- Alessandra Ori – Clinical Operation Manager
- Sara Rizzoli - Biostatistician
- Saide Sala – Clinical Operation Specialist
- Simona Sgarbi –Business Development & Study Design Manager
- Lucia Simoni –Clinical Data Management and Biostatistics Unit Manager
- Francesca Trevisan – Site Support Specialist
- Giovanni Fiori- President and Scientific Director

## References

1. Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, et al; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009;27:6251-66.
2. Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, et al; American Society of Clinical Oncology. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2011;29:3825-31.
3. Vansteenkiste J, De Ruyscher D, Eberhardt WE, et al; ESMO Guidelines Working Group. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi89-98.
4. Reck M, Popat S, Reinmuth N, et al; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25 Suppl 3:iii27-39.
5. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
6. Barni S, Venturini M, Beretta GD, et al; AIOM Guidelines Task Force. Agreement between oncology guidelines and clinical practice in Italy:

the 'right' program. A project of the Italian Association of Medical Oncology (AIOM). Ann Oncol 2007;18 Suppl 6:vi179-84.

7. Barni S, Venturini M, Molino A, et al. Importance of adherence to guidelines in breast cancer clinical practice. The Italian experience (AIOM). Tumori 2011;97:559-63.
8. I numeri del cancro in Italia 2014. AIOM – AIRTUM. Intermedia Editore, 2014. Available online [www.aiom.it](http://www.aiom.it), last accessed April 15<sup>th</sup>, 2015.
9. Linea Guida AIOM 2009 – Neoplasie polmonari. Available online [www.aiom.it](http://www.aiom.it), last accessed July 22<sup>nd</sup>, 2015
10. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-714.
11. Audet AM, Greenfield S, Field M. Medical practice guidelines: current activities and future directions. Ann Intern Med 1990;30:709-714.
12. Kassam F, Shepherd FA, Johnston M, et al. Referral patterns for adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. J Thorac Oncol 2007;2:39-43.
13. Kankesan J, Shepherd FA, Peng Y, et al. Factors associated with referral to medical oncology and subsequent use of adjuvant chemotherapy for non-small-cell lung cancer: a population-based study. Curr Oncol. 2013;20:30-7.

14. Banna GL, Di Maio M, Follador A, Collovà, et al; ISA Co-Authors. Italian Survey on adjuvant treatment of non-small cell lung cancer (ISA). *Lung Cancer* 2011;73:78-88.
15. Kankesan J, Shepherd FA, Peng Y, et al. Factors associated with referral to medical oncology and subsequent use of adjuvant chemotherapy for non-small-cell lung cancer: a population-based study. *Curr Oncol* 2013;20:30-7.
16. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181-90.
17. Ramella S, Maranzano E, Frata P, et al. Radiotherapy in Italy for non-small cell lung cancer: patterns of care survey. *Tumori* 2012;98:66-78.
18. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1999;91:66-72.
19. Gridelli C, Perrone F, Gallo C, et al; MILES Investigators. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003;95:362-372.
20. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;304:2245-52.

21. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458-65.

## **Figure legends**

**Figure 1.** Histology at diagnosis by stage

**Figure 2.** First-line treatment (for Stage IIIB and IV patients)